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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/682,192	**Applicant(s)** CHIUEH ET AL.	
	Examiner Hong Sang	**Art Unit** 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I (claims 1-13 and 17-19) in the reply filed on 4/25/2006 is acknowledged.

2. Claims 1-19 are pending. Claims 14-16 are withdrawn from further consideration as being drawn to non-elected inventions.

3. Claims 1-13 and 17-19 are under examination.

Drawings

4. It appears that the 1st peak (dark color area), in Fig.1, should be the control group without phycoerythrin, and the 2nd peak (light color area) should be the experiment group with phycoerythrin because cells with phycoerythrin would expect to produce higher fluorescence intensity.

Claim Objections

5. Claim 17 is objected to as being dependent on a non-elected claim.

6. Claim 12 is objected to because the claim recites alternatives in incorrect format. A Markush-type claim should recite alternatives in a format such as "selected from the group consisting of A, B and C." See MPEP § 803.02. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-13, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-13, 18 and 19 are indefinite for reciting the phrase "range of tumor tissues or cells" in claim 1. The meaning of the phrase "range of tumor tissues or cells" is unclear. Does it mean the size of the tumor? Or does it mean tumor metastases?

B. Claim 1-13, 18 and 19 are indefinite for reciting the phrase "a certain period" in claim 1. The meaning of the phrase "a certain period" is unclear. Does it mean a certain period of time?

C. Claim 11 is indefinite for reciting the term "liquid tumor". The meaning of the "liquid tumor" is unclear. Does it mean blood cancer such as leukemia?

D. Claim 19 is indefinite for reciting the phrase "immunofluorescence staining" on line 3 of the claim. How is the level of fluorescent staining of tumor to be analyzed by immunofluorescence staining? Does it mean immuno-detection or fluorescence detection?

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-13 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for labeling tumor tissues or cells in vitro by utilizing R-phycoerythrin or B-phycoerythrin, does not reasonably

provide enablement for a method for labeling tumor tissues or tumor cells in vivo by utilizing all phycoerythrin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims are drawn to a method for labeling tumor tissues or cells by utilizing phycoerythrin.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The method encompasses in vitro and in vivo labeling of tumor tissues or cells using all phycoerythrin.

Quantity of experimentation

The quantity of experimentation in this area is extremely large because the claims encompass a genus of tumors and a genus of phycoerythrin. It would require significant study to determine which tumor can in fact be selectively labeled in vivo by phycoerythrin. Moreover, the phycoerythrin includes any and all art known and unknown phycoerythrin. It would require significant study to determine which phycoerythrin is in fact capable of specifically target and label the tumor tissue or cell, for example a brain tumor.

The unpredictability of the art and the state of the prior art

The instant specification teaches that R-phycoerythrin and B-phycoerythrin can selectively label various tumor cells in vitro. The prior art teaches that R-phycoerythrin and the subunits thereof can enter mouse tumor cell S180 (in vitro), human liver carcinoma cell SMC7721 (in vitro), and a mouse tumor in vivo, wherein the S180 tumor cells were treated with R-phycoerythrin before they were inoculated in forelimb, i.e. the tumor cells were treated with R-phycoerythrin or subunits thereof in vitro (see Bei et al. Cancer Biotherapy & Radiopharmaceuticals, 2002, 17(1): 35-42, see page 36, left column, 2nd paragraph and right column, last paragraph). Bei et al. teach that the critical target for photodynamic damage is most probably located intercellularly, therefore, the capacity of photosensitizer to enter the target cell is an important parameter in photodynamic therapy (PDT) efficacy (see page 40, middle section). The prior art does not teach that R-phycoerythrin or B-phycoerythrin can be delivered to the solid tumor cells in vivo, particularly deep tumor cells. Moreover, the instant specification does not provide guidance on the in vivo delivery of R- or B-phycoerythrin into a solid tumor.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, in vivo drug delivery is at most unpredictable. For example, Jain (Scientific American July 1994) discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Working examples

The specification teaches that R-phycoerythrin and B-phycoerythrin selectively recognize and enter various tumor cells in vitro (see Example 1, and Table 2). The specification teaches that phycoerythrin selectively recognize and enter the leukemia cells not normal blood cells in vitro (see Example 3). The specification teaches the tumor cells labeled with R- and B-phycoerythrin can be detected by flow cytometry or fluorescence microscope (see Example 3 and Figs. 3&4). However, the specification fails to show that all tumor cells can be labeled in vivo by phycoerythrin.

Guidance in the specification

The specification provides no guidance on in vivo delivery of phycoerythrin to tumor tissue or cell. The specification provides no guidance on in vivo exposing tumor cells with light. Moreover, the specification provides no guidance on how to monitoring the fluorescence in vivo to identify the tumor location and tumor stage, particularly using flow cytometry to monitor the tumor stage (see claims 18 and 19). The specification does not teach how to correlate the fluorescence to the tumor stage.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example that any phycoerythrin would label the tumor cells in vivo and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-6, 8-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bei et al. (Cancer Biotherapy & Radiopharmaceuticals, 2002, 17(1): 35-42) in view of the teachings of Dougherty et al. (J. National Cancer Institute, 1998, 90(12): 889-905), Li et al. (Shengwu Huaxue Yu Shengwu Wuli, 2000, 27(6): 621-624, abstract only) and Oi et al. (J. Cell Biol., 1982, 93: 981-986).

Claims are drawn to a method for labeling tumor tissues or cells by utilizing R-phycoerythrin comprises the steps of: adding effective amount of phycoerythrin to tissues or cells in vitro and incubating for a certain period; exposing said tissue or cells containing effective amount of phycoerythrin with appropriate wavelength of light to stimulate phycoerythrin to emit fluorescence; and monitoring said fluorescence to identify the location of tumor tissues or cells. The methods are further limited wherein the length of said certain period of incubation varies according to cell types, generally from 0.5 hr to 24 hr, said wavelength of light is between 488 and 633 nm, the wavelength for stimulating R-phycoerythrin is at 488 nm, said effective amount of phycoerythrin is between 0.5-10 ug/ml, the fluorescence is monitored at wavelength above 565 nm, the tumor is solid tumor, the tumor is hepatoma, said labeling tumor tissues or cells means that the tumor-recognizing and tumor-entering ability of phycoerythrin is utilized in order to achieve the performance of labeling tumor tissues or cells.

Bei et al. teach a method for treating cancer cells including human liver carcinoma cells and mouse S180 tumor using R-phycoerythrin, comprising treating the tumor cells with 10-100ug/ml of R-phycoerythrin for 4hr and exposing the treated tumor cells to a 496 nm Argon laser (see page 36, left column, 2nd paragraph, right column, 1st paragraph and last paragraph).

Bei et al. do not teach monitoring the fluorescence to identify the location of tumor tissues or cells. Bei et al. do not teach that the wavelength for stimulating R-phycoerythrin is at 488 nm, and fluorescence is monitored at wavelength above 565 nm.

However, these efficiencies are made up for in the teachings of Dougherty, Li and Oi et al.

Dougherty et al. teach photodynamic therapy wherein a tumor-localizing photosensitizing agent is administered to the tumor cells, followed by activation of the agent by light of a specific wavelength (see abstract). Dougherty et al. teach that as new sensitizers are prepared, studies on localization, both at a tissue and a subcellular level, can be carried (see page 889, right column, 2nd paragraph). Dougherty et al. teach that since most photosensitizing agents are fluorescent, drug localization can be determined by fluorescence microscopy (see page 890, line 3-4).

Li et al. teach that a method of treating a cancer cell comprising administering R-phycoerythrin to the cell, and illuminating the cell with a laser at wavelength 488 nm laser (see abstract).

Oi et al. teach the absorption and fluorescent emission wavelength for R-phycoerythrin (see Table 1 and Figure 1). Oi et al. teach that the maximum emission wavelength is 578 nm. Oi et al. teach fluorescence-activated cell sorting analysis of human peripheral blood lymphocytes labeled with phycoerythrin (see Figure 3). While Oi does not teach the specific 565 nm, it is considered as an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bei and/or Li by including a step of detecting the level of the fluorescence generated from the labeled tumor cells at the wavelength of 565 nm in view of the teachings of Dougherty and Oi. One would have been motivated to modify the method of Bei and/or Li by including a step of detecting the level of the fluorescence generated from the labeled tumor cells at the wavelength of 565 nm because Dougherty teaches by detecting the fluorescence generated from the labeled tumor cells, one can identify the drug location both at a tissue and a subcelluar level, therefore one can specifically activate and damage the labeled tumor cells by light, and Oi teaches that the maximum emission wavelength for R-phycoerythrin is 578 nm. One of ordinary skill in the art would have a reasonable expectation of success to modify the method of Bei and/or Li by including a step of detecting the level of the fluorescence generated from the labeled tumor cells at the wavelength of 565 nm because detection the level of the fluorescence in a cell by fluorescence microscopy or flow cytometry is well known in the art as shown by the teachings of Oi.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER**

Hong Sang
Art Unit 1643
May 15, 2006